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Prognostic factors and patterns of recurrence in esophageal cancer assert arguments for extended two-field transthoracic esophagectomy

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KEYWORDS:
Prognostic factors;
Recurrence pattern;
Transthoracic esophagectomy;
Extended lymphadenectomy

Abstract

BACKGROUND: High recurrence rates determine the dismal outcome in esophageal cancer. We reviewed our experiences and defined prognostic factors and patterns of recurrences after curatively intended transthoracic esophagectomy.

METHODS: Between January 1991 and December 2005, 212 consecutive patients underwent a radical transthoracic esophagectomy with extended 2-field lymphadenectomy. Recurrence rates, survival, and prognostic factors were analyzed (minimal follow-up period, 2 y).

RESULTS: Radicality was obtained in 85.6%. The median follow-up period was 26.6 months. The overall recurrence rate at 1, 3, and 5 years was 28%, 44%, and 64%, respectively, and locoregional recurrence rate was 17%, 27%, and 43%, respectively. Overall survival rates, including postoperative deaths, were 45% and 34% at 3 and 5 years, respectively. pT stage and lymph node (LN) ratio greater than .20 were independent prognostic factors for survival and recurrences. Radicality was most prognostic for survival, and for N+ greater than 4 positive LN for recurrences.

CONCLUSIONS: Radicality and LN ratio are strong prognostic factors. High radicality and adequate nodal assessment are guaranteed by an extended transthoracic approach.

Annually, more than 1,500 new patients are diagnosed with esophageal cancer in The Netherlands and 460,000 new patients worldwide and the incidence still is increasing.[1,2] The tumors are difficult to treat as reflected by a relatively low yearly rate in curatively intended treated patients of 40%. Over the years different treatment modalities have been proposed but surgical resection remains the mainstay of treatment.[3,4] Even with significant advances in the surgical techniques and perioperative treatment, the 5-year survival rate after curative intended surgery rarely is greater than 25%.[5] One of the important reasons is a relatively high recurrence rate of more than 50% in these patients, leading to an ongoing debate about the optimal surgical procedure, eventually with a neoadjuvant

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combined treatment modality, regarding better local tumor control, prognosis, and survival.[6–8]

Although the extended 2-field transthoracic esophagectomy has been associated with lower locoregional recurrences, it has not yet translated into significantly better survival compared with the less-extensive transhiatal blunt dissection.[9,10] However, a recently performed randomized Dutch study by Hulscher et al[9] and the updated results showed a trend toward a better survival for the transthoracic approach, even in the distal region.[11] The rationale of the extended transthoracic method, which is the recommended procedure in our center, is to diminish local recurrences by providing an optimal local radicality, eradicating regional (micro)metastases, which occur frequently in esophageal cancer. Therefore, we investigated the impact of radicality of surgery on survival, patterns of recurrences, and different prognostic factors in a relatively large, equally staged and treated, group of patients, who underwent a curatively intended esophageal resection with a standard 2-field lymphadenectomy in our hospital during a 15-year period.

We compared our data with the results of several large series in the literature about the quality of surgery regarding radicality to obtain better insight in the prognostic factors for recurrence and survival in these patients.

Patients and Methods

Patients

Between January 1991 and December 2005, a total of 220 consecutive patients with histologically proven cancer of the esophagus and gastroesophageal junction underwent a curative intended radical transthoracic resection with an extended 2-field lymph node dissection (2-FLND).

The database of these patients included demographic information; tumor characteristics such as tumor size, grade, histology, stage, therapeutic information; and survival data collected prospectively during the follow-up evaluation. Informed consent was obtained in all patients with approval from the institutional ethical board. In this study we excluded patients (n = 8) with high-grade dysplasia (carcinoma in situ) from the analyses.

Except from the overall survival calculations, we also excluded those with macroscopic irradicality (n = 1), the so-called *R2 resections* according to the International Union Against Cancer Classification,[12] and those who died within 30 days or in-hospital (n = 9; 4.1%).

Consequently, we analyzed 212 patients in the survival calculations, most (85%) had adenocarcinomas. Eight of the 10 excluded patients (from recurrences analyses) had stage III tumors, whereas the other 2 excluded patients had stage II tumors. Microscopic radical resection (R0) was achieved in 87% (186 of 212). The average number of resected nodes was 11 (standard deviation, 8.1; range, 3–61; median, 10). The median follow-up period was 26.6 months (standard deviation, 41.1 mo; range; .13–197 mo).

In the recurrence analyses (n = 202), 16 patients (7.9%) received neoadjuvant chemoradiotherapy. The male:female ratio was 4.8:1, with a median age of 63.5 years. In this group, 174 patients (86.1%) had an adenocarcinoma and most tumors were located in the distal part of the esophagus (55.9%, n = 113; Table 1). Generally, the tumors (n = 132; 65.3%) were locally advanced T3 or resectable T4 tumors and more than half of the patients (56.9%: n = 115) had regional node metastases. Of these patients, 13 (11.3%) had distant nodal M1a metastasis. The most frequently performed approach was through a left thoracolaparotomy with an intrathoracic anastomosis. R0 resection was achieved in 181 patients (181 of 202; 89.6%).

Methods

Preoperative staging procedure. The preoperative work-up consisted of an endoscopic ultrasonography with eventual fine-needle aspiration of pathologic nodes that would change the preoperative staging (N0 vs N+ and M0 vs M1a); a 16 to 64 multislice multidetector computed tomography (CT) scan of the neck, chest, and abdomen; and ultrasonography of the cervical region to rule out tumors that were locally nonresectable or distant metastases (M1b). Since the introduction of 18F-fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET) scan in our hospital (1996), patients with a T3 or resectable T4 and/or N1 tumor had an additional FDG-PET.[13] After the clinical work-up all patients were discussed at a multidisciplinary panel.

Surgical approach. All patients underwent an extended transthoracic resection by the same surgical group. The surgical procedure started with a laparotomy exploring the peritoneal cavity to exclude distant metastatic disease (M1b) or local nonresectability (T4). Resection was performed through a left thoracolaparotomy with intrathoracic anastomosis in case of lower-third esophageal and gastroesophageal junction tumors, as categorized by Siewert et al[14] or through a right thoracolaparotomy with cervical anastomosis in squamous cell tumors and the more proximal adenocarcinomas, including all Barrett tumors.

Routinely, we performed an en bloc esophagectomy with a 2-FLND of the mediastinal and abdominal nodes, including the nodes at the celiac trunk, along the common hepatic artery and upper border of the pancreas, and the para-aortic regional nodes. Reconstruction usually consisted of a gastric tube, vascularized on the right gastroepiploic vessels, or a colonic substitute in case of previous gastric surgery.

Pathologic assessment. The resected specimens were examined according to the standard pathologic procedures. Depth of tumor invasion (pathologic or pT stage), nodal involvement, and distal and proximal resection margins were examined routinely and we reported the presence of lymph/angio invasion and perineural invasion. The 6th International Union Against Cancer Classification/TNM classification was the basis for pathologic staging in these

Table 1 Clinicopathologic characteristics of patients divided into recurrent and nonrecurrent groups

Characteristic	Recurrence (n = 119)	No recurrence (n = 83)	*P* value
Sex, male/female	99/20 (83.2)	68/15 (81.9)	.816
Median age, y	62.0/28.8–80.9	66.7/41.1–81.8	**.038**
Localization, %			.540
Mid/upper	9 (7.6)	8 (9.6)	
Distal	66 (55.5)	47 (56.6)	
GEJ	44 (37.0)	28 (33.7)	
Histology, %			.537
Adenocarcinoma/SCC	104/15 (87.4)	70/13 (84.3)	
Type of resection, %			.992
Left TT/right TT	63/56 (52.9)	44/39 (53.0)	
Anastomosis site, %			.689
Intrathoracic/cervical	75/44 (63.0)	50/33 (60.2)	
Pathologic T stage, %			**<.001**
T1	3 (2.5)	24 (28.9)	
T2	17 (14.3)	26 (31.3)	
T3	89 (74.8)	29 (34.9)	
T4	10 (8.4)	4 (4.8)	
Pathologic N stage, %			**<.001**
N0/N1	33/86 (27.7)	54/29 (65.1)	
Pathologic M stage, %			.052
M0/M1a	108/11 (90.8)	81/2 (97.6)	
Tumor stage, %			**<.001**
I	3 (2.5)	22 (26.5)	
IIa	28 (23.5)	29 (34.9)	
IIb	9 (7.6)	12 (14.5)	
III	69 (58.0)	18 (21.7)	
IVa	10 (8.4)	2 (2.4)	
Radicality, %			**.009**
R0/R1	101/18 (84.9)	80/3 (96.4)	
>4 Positive nodes, %			**<.001**
Yes/no	33/86 (27.7)	3/80 (3.6)	
>.20 Ratio of positive nodes, %			**<.001**
Yes/no	61/58 (51.3)	13/70 (15.7)	
Perineural invasion, %			**<.001**
Yes/no	37/82 (31.1)	8/75 (9.6)	
Lymphangio invasion, %			**<.001**
Yes/no	43/76 (36.1)	13/70 (15.7)	
Adjuvant therapy, %			.174
Yes/no	12/107 (10.1)	4/79 (4.8)	

GEJ = gastroesophageal junction; SCC = squamous cell carcinoma; TT = transthoracic.
Bolded entries in tables indicate the significant values.

patients.[15] Based on the prognostic significance in the literature we also incorporated the number of resected nodes, the presence of more than 4 positive lymph nodes, and the ratio of positive nodes to the total number of resected lymph nodes in the pathologic staging reports.[16]

Follow-up evaluation and survival. Patients were followed up every 3 months for the first postoperative year, every 6 months for the next year, and then annually for 10 years. The last follow-up evaluation was in January 2008, ensuring a minimum of 2 years of follow-up evaluation. All data were collected prospectively in a patient research database.

Relevant information regarding the follow-up evaluation was collected from our research database, medical records, general practitioners, and data from the Comprehensive Cancer Center North Netherlands. The follow-up period was calculated from the time of resection until death from any cause or last follow-up evaluation (the overall survival [OS]). Disease-free survival was calculated from the time of surgery until recurrence, last follow-up evaluation, or death from any cause.

Recurrence definition. Any cytologic or histologic proof, unequivocal or strong radiologic (CT, magnetic resonance imaging, PET, bone scan, and ultrasonography) suspicious lesions, or obvious clinical evidence of tumor was regarded as recurrent disease. Recurrences were classified in 3 categories: local, regional, and distant disease. Depending on the location of the primary tumor, local recurrence at the anastomotic site was defined as cancer recurrence at the anastomosis or at the whole upper mediastinum for upper- and midesophageal tumors and for distal and gastroesophageal junction tumors as recurrence at the anastomosis or at the

Table 2 Locoregional recurrence

Primary localization of tumor	N (%)
Mid/upper (n = 17)	
Anastomotic	3 (17.6)
Mediastinal	4 (23.5)
Distal/GEJ (n = 185)	
Anastomotic	30 (16.2)
Mediastinal/hiatal	24 (13.0)
Regional recurrences	9

GEJ = gastroesophageal junction.

distal mediastinum and hiatal region. Regional recurrence was defined as nonlocal recurrences within the 2-field area. Distant recurrence was categorized according to the involved organ in hepatic, pulmonary, skeletal, cerebral, skin or soft tissue, and peritoneal metastases. Any additional recurrence found within 6 weeks of the first recurrence was considered to have occurred simultaneously.

Treatment of recurrence. Depending on the presenting complaints, site, and type of recurrences, treatment was considered palliative or having curative intent. In case of a localized or locoregional recurrence treatment with curative intention was offered to the patient whenever possible. The decision to treat was addressed in a multidisciplinary discussion in close collaboration with the surgeon, medical oncologist, gastroenterologist, and radiotherapeutic oncologist. As reported previously by our group, treatment consisted of best supportive care, radiotherapy alone or combined with chemotherapy, chemotherapy alone, or stenting.[17] Different combinations of these treatment modalities also were given. Curatively, intended radiotherapy usually was given in doses of 50 to 60 Gy and/or in combination with 5-fluorouracil and cisplatin.

Statistical analysis. Continuous variables were compared with the *t* test and categoric variables were compared with the chi-square test. Survival and recurrence rates were calculated according to the Kaplan–Meier method and if applicable were compared using the log-rank test. Univariate and multivariate Cox regression analyses were performed to identify prognostic factors for survival and recurrent disease. Factors with a P value of less than .1 in the univariate analysis were included in the multivariate Cox regression analysis. A P value of less than .05 (95% confidence interval) was considered significant. The statistical analyses were performed by using the Statistical Package for Social Sciences (SPSS) version 14.0 software, Chicago, IL.

Results

Recurrences

During the follow-up period recurrent disease was observed in 119 patients (58.9%; Table 1). The diagnosis of recurrence was based mainly (92%) on radiologic evidence of disease (CT, magnetic resonance imaging, bone scan, FDG-PET, or ultrasonography) or confirmed by histologic or cytologic examination during endoscopy. In 10 patients the diagnosis of recurrent disease was based solely on clinical evidence of disease without further diagnostic examinations.

As shown in Table 1, the 202 patients were divided into 2 groups; the recurrence group (n = 119) and the nonrecurrence group (n = 83). Sex, histology, localization, type of resection, anastomotic site, M stage, and adjuvant therapy did not differ significantly between the groups.

Patients with recurrent disease generally were younger than those without recurrent disease, 62.0 versus 66.7 years (P = .038), respectively. The tumors in the recurrence group had a more advanced tumor invasion (pT stage), and more often involvement of more than 4 locoregional lymph nodes. In addition, an LN ratio of more than .20 was significantly more prevalent in patients with recurrent tumors. Furthermore, perineural and lymphangio invasion were encountered more often, and at pathologic examination a microscopically involved surgical resection margin (R1) was found more often.

The overall recurrence rates at 1, 3, and 5 years after resection were 28%, 44%, and 64%, respectively, whereas locoregional recurrence rates (LRR) occurred in 17%, 27%, and 43%, respectively.

Table 2 shows the LRR site classified according to the primary tumor localization. Distant recurrent disease (Table 3) occurred frequently in the liver (33%) and the skin or soft tissue (40.3%). One of the soft-tissue recurrences was located in the orbital region. Cerebral recurrences were diagnosed relatively often (5.6%).

Survival

The patients (n = 212), including those who died postoperatively (n = 9), in this study had a crude OS of 74%, 45%, and 34% after 1, 3, and 5 years, respectively (Fig. 1). The 10-year OS rate was 27%. When we include only those who had a successful resection (n = 202), the crude OS rate was 78%, 47%, and 36% after 1, 3, and 5 years, respectively.

Patients without recurrences had a significantly higher 5-year survival rate than those who developed recurrent disease; 73% and 8%, respectively (Fig. 2; $P = < .001$).

Table 3 Hematogenous recurrence site (n = 72)

Hematogenous recurrence	N (%)
Liver	24 (33.3)
Lung	10 (13.8)
Bone	18 (25.0)
Cerebral	4 (5.6)
Skin or soft tissue	29 (40.3)
Peritoneal	18 (25.0)

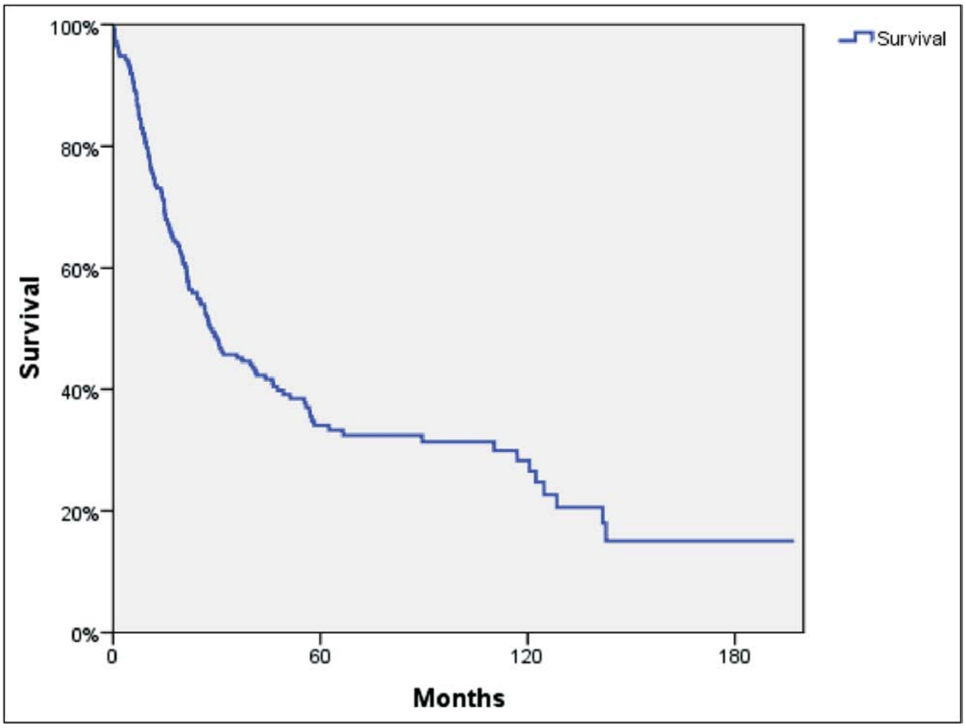

Figure 1 Kaplan–Meier analysis: OS in 212 patients.

Prognostic factors for survival and recurrent disease

Prognostic factors for survival from the univariate analysis were pT stage (pT2 hazard ratio [HR], 4.7; pT3 HR, 11.4; and pT4 HR, 21.7), pN stage (HR, 3.1), pM stage (HR, 2.3), outcome (HR, 2.4), more than 4 positive lymph nodes (HR, 2.3), positive lymph node ratio greater than .20 (HR, 3), perineural invasion (HR, 1.8), and lymphangio invasion (HR, 1.7). Independent prognostic factors for survival and recurrent disease are displayed in Table 4. Factors that were

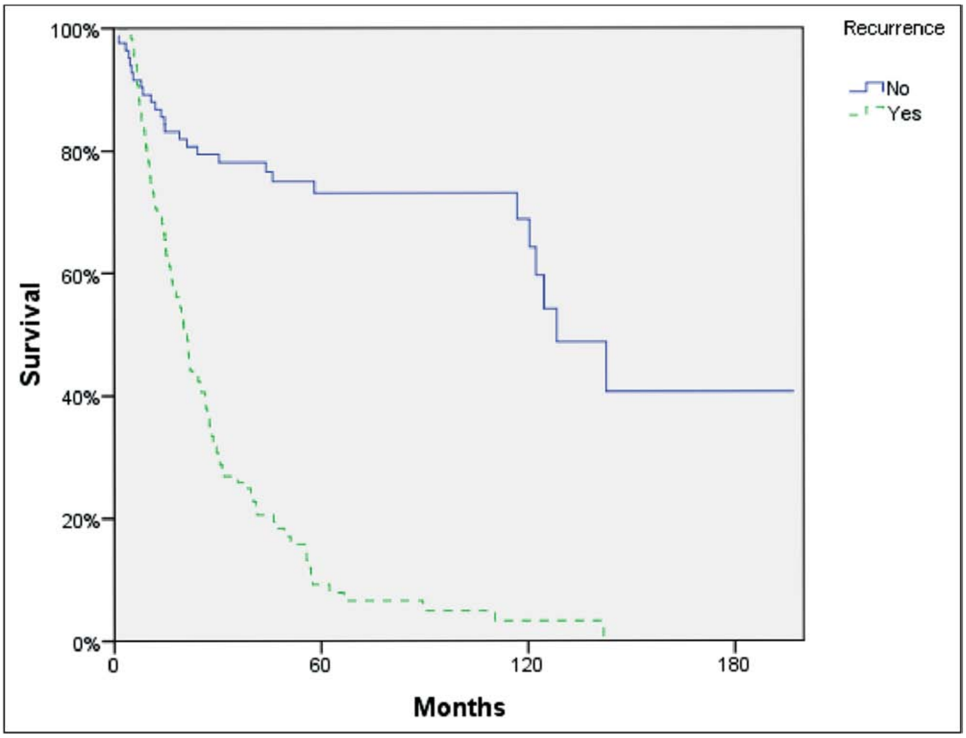

Figure 2 Kaplan–Meier analysis for 202 patients: survival for the recurrence and nonrecurrence groups.

not significant for both survival and recurrent disease were pN stage, pM stage, outcome, perineural invasion, and lymphangio invasion.

Prognostic factors for recurrent disease from the univariate analysis were pT stage (pT2 HR, 5.2; pT3 HR, 13.8; and pT4 HR, 20.4), pN stage (HR, 3.5), pM stage (HR, 3.1), outcome (HR, 2.5), more than 4 positive lymph nodes (HR, 4.9), positive lymph node ratio greater than .20 (HR, 3.8), perineural invasion (HR, 2.3), and lymphangio invasion (HR, 2.1).

Of the dependent factors that are displayed in Table 5, the pT3/T4, radicality (R0 vs R1), lymph node ratio greater than .20, and perineural invasion were independent prognostic factors for LRR (Table 6). In both the univariate and multivariate analyses pT1 versus pT2 was not significant.

Year of surgery was not prognostic for survival (P = .632) or recurrence (P = .926) in the univariate analyses.

Comments

The results of this study show that a transthoracic esophagectomy with 2-FLND provides good disease control in patients with esophageal cancer. Usually, better results can be achieved in high-volume centers with experienced surgeons generally implementing an uniform treatment policy. The reported 5-year survival rate in the literature rarely exceeded 25%.[5] In this study the 5-year OS with and without the postoperative deaths was 34% and 36%, respectively, which is in concordance with reported results in other experienced centers.[9–11,18] Our results confirm that a transthoracic extended procedure remains an important curative option in the surgical treatment of these patients.

The reported early OS rate at 1 and 3 years as well as the late 5- and 10-year OS rates in this study are relatively high at 74% and 45% and 34% and 27%, respectively. Considering that most patients (65.3%) had a T3 tumor or higher stage, the high-grade dysplasia or in situ cancers were excluded but locoregional M1a tumors were included, one should agree that these figures are in line with those of

Table 4 Multivariate Cox regression analysis: independent prognostic factors for survival (n = 212) and recurrent disease (n = 202) after extended esophagectomy for carcinoma of the esophagus

Survival	HR	95% Confidence interval Lower	95% Confidence interval Upper	P value
pT stage, compared with T1				
pT2	3.988	1.361	11.691	**.012**
pT3	8.518	3.170	24.120	**<.001**
pT4	17.280	4.447	43.347	**<.001**
Outcome	1.706	1.071	2.616	**.024**
Lymph node ratio >.20, yes vs no	2.550	1.593	3.180	**<.001**
Recurrence				
pT stage, compared with T1				
pT2	4.287	1.250	14.708	**.021**
pT3	9.775	3.042	31.416	**<.001**
pT4	16.625	4.430	62.395	**.001**
>4 Positive lymph nodes, yes vs no	2.361	1.411	3.952	**.001**
Lymph node ratio >.20, yes vs no	2.004	1.271	3.159	**.003**

Bolded entries in tables indicate the significant values.

Table 5 Univariate Cox regression analysis: prognostic factors for locoregional recurrent disease after extended esophagectomy for carcinoma of the esophagus (n = 202)

Factor	HR	95% Confidence interval Lower	95% Confidence interval Upper	P value
pT stage, compared with T1				
pT3	11.531	2.765	48.091	**.001**
pT4	16.596	2.698	102.067	**.002**
pN stage, negative vs positive	3.716	2.005	6.889	**<.001**
pM stage, negative vs positive,	3.655	1.297	10.304	**.014**
Outcome, R0 vs R1	4.832	2.533	9.217	**<.001**
>4 Positive lymph nodes, yes vs no	8.1	4.351	14.967	**<.001**
Lymph node ratio >.20, yes vs no	5.417	3.017	9.727	**<.001**
Perineural invasion, yes vs no	2.907	1.497	5.645	**.002**
Lymphangio invasion, yes vs no	3.184	1.773	5.719	<.001

Bolded entries in tables indicate the significant values.

Table 6 Multivariate Cox regression analysis: independent prognostic factors for locoregional recurrent disease after extended esophagectomy for carcinoma of the esophagus (n = 202)

Factor	HR	95% Confidence interval Lower	95% Confidence interval Upper	P value
pT stage, compared with T1				
pT3	6.221	1.424	27.173	**.015**
pT4	7.627	1.165	49.918	**.034**
Outcome, R0 vs R1	3.627	1.516	5.901	**.002**
Lymph node ratio >.20, yes vs no	3.627	1.958	6.717	**<.001**
Perineural invasion, yes vs no	2.010	.999	4.047	**.050**

Bolded entries in tables indicate the significant values.

expert centers. The study by Portale et al[19] reported a higher survival rate of 50%, but the patient population consisted of a large group of stage I tumors (37%), compared with 13.4% in our study.

The rate of microscopic radicality expressed as a R0 resection was 89.6%, which resulted in a rate of LRR of 21% (n = 41) in the resected tumors, which is relatively low, particularly in the light of the low number of neoadjuvant-treated patients in this group (7.9%). Usually the reported microscopic radicality (R0 resection) rate is between 57% and 72%.[9,20] The relatively high rate of R0 resections in our study (84.9%) can be explained by the standard transthoracic surgical procedure with a 2-FLND. Surgeons who routinely performed a transthoracic esophagectomy had better survival outcomes for their patients.[21] In a previous reported comparative study in the northern part of The Netherlands we showed improved treatment results at the University Hospital in comparison with other teaching and nonteaching hospitals in the region.[22] Moreover, as established in the present study, the radicality of the surgical procedure was an independent prognostic factor for locoregional recurrences. This is expected from what is known in the literature on the effect of R0 resections.[8,12] Despite a high R0 resection rate the overall 5-year recurrence rate was disappointing in this and other studies, providing additional arguments for the use of neoadjuvant treatment modalities. In the meta-analyses of Gebski et al[23] neoadjuvant treatment was strongly suggested to achieve a higher number of R0 resections, increasing locoregional control. The literature overview in Table 7 arguments the importance of radicality (R0) obtained by extended surgical resection. Currently, neoadjuvant chemoradiation contributes considerably in these efforts, preventing the occurrence of LRR.

Otherwise, radiotherapy eventually combined with chemotherapy was considered as the treatment of choice in recurrent disease, which was used in 48% of our patients with recurrent disease. Studies have shown that aggressive radiotherapy treatment could be beneficial for survival and local control, reducing dysphagia.[24,25] This approach may contribute to the relatively high OS rate in our total study population. The recurrence group consisted of younger patients ($P = .038$). An explanation for this observation may be the presentation of more advanced disease and a delayed diagnosis.[26]

The outcome of surgery in patients with a positive lymph node ratio (LNR) of more than .20 is a strong prognostic factor for a worse survival. In a review article Lagarde et al[27] found the LNR and number of positive lymph nodes to be of strong prognostic value for the survival rate. Dependent prognostic factors for recurrent disease were pT stage, outcome of surgical margin, more than 4 positive lymph nodes, positive LNR greater than .20, perineural invasion, and lymphangio invasion. Independent prognostic factors for recurrent disease were pT stage, more than 4 positive lymph nodes, and positive LNR greater than .20.

Our findings show single-institute data for the surgical treatment of esophageal cancer with good insights into the prognostic factors for recurrent disease.

A possible weakness of this study was that the follow-up period was based primarily on clinical symptoms followed by further investigation when necessary and not on routinely based radiologic examinations. Determination of the moment of recurrent disease as accurately as possible (lead time bias) is important for calculating the disease-free survival used in the regression analysis for recurrent disease. Because we did not implement radiologic examinations routinely during follow-up evaluation our lead time could be confounding. However, it could be reduced to a minimum by including patients in a thorough follow-up scheme.

By incorporation of more than 4 positive lymph nodes and more than a .20 positive lymph node ratio into the staging procedure one can predict the prognoses more accurately and adjust the treatment accordingly. This is not a new idea because recently published studies also advocated to determine these factors routinely.[16] We believe that this study adds important information to this concept.

Figure 1 clearly shows the impact of recurrence on survival ($P < .001$). It is therefore important to understand

Table 7 Literature overview

Study	Number of patients	Mortality, in-hospital and 30 day	Histology	R0 rate	Survival, y
Mariette et al,[18] 2003	439	4.5% (in-hospital) 2.4% (30 day)	AC 17.5%	Only R0	3; 54% 5; 41%
Altorki and Skinner,[10] 2001	111	5.4%	AC 73%	97.3%	5; 40%
Omloo et al,[11] 2007			Only AC		
THE	95	2%		72%	5; 34%
TTE	110	7%		72%	5; 36%
Nakagawa,[28] 2004	171	1.7% (30 day)	Only SCC	96%	5; 55.6%
Dresner and Griffin,[7] 2000	176	4% (in-hospital) 2% (30 day)	AC 64%	Only R0	1; 83% 5; 31%
Present study, 2009	212	4.1%	AC 85%	87%	1; 74% (78%)* 3; 45% (47%) 5; 34% (36%)

AC = adenoca; SCC = squamous cell cancer; THE = transhiatal resection; TTE = transthoracic resection.
*Excluding postoperative mortality.

what factors predict recurrence. This study described these factors and therefore clinicians can predict which patients are more likely to have a recurrence more accurately than based solely on the TNM.

Conclusions

Extended radical resections through a transthoracic approach provide relatively good local control with high early and late survival. Nodal involvement, including more than 4 positive lymph nodes and a LNR greater than .20 are strong prognostic factors for recurrent disease, particularly locoregional recurrences. This study also showed that the quality of surgery is an independent significant factor affecting both recurrences and survival.

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